PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AXP/PG4792	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/03343	International filing date *(day/month/year)* 27.03.2003	Priority date *(day/month/year)* 28.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D265/30		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.09.2003	17.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Scruton-Evans, I Telephone No. +49 89 2399-8272

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03343

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-26 as originally filed

Claims, Numbers

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: KATO S ET AL: 'NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTRIC PROKINETIC AGENTS 1. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF N-(2-MORPHOLINYL)ALKYLBENZAMIDES' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 33, no. 5, May 1990 (1990-05), pages 1406-1413, XP001037844 ISSN: 0022-2623

D2: WO 02 26723 A (HARRISON LEE ANDREW ;JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) cited in the application

D3: EP-A-0 995 746 (YOSHITOMI PHARMACEUTICAL) 26 April 2000 (2000-04-26)

D4: DE 24 47 732 A (WUELFING J A FA) 8 April 1976 (1976-04-08)

D5: MORIE T ET AL: 'ASYMMETRIC SYNTHESIS OF THE ENANTIOMERS OF 2-AMINOMETHYL-4-(4-FLUOROB ENZYL)MORPHOLINE, AN INTERMEDIATE OF MOSAPRIDE, A GASTROPROKINETIC AGENT' HETEROCYCLES, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 38, no. 5, 1994, pages 1033-1040, XP001037848 ISSN: 0385-5414

D6: MORIE T ET AL: 'Synthesis and Biological Activities of the Optical Isomers OF (PLUS MINUS)-4-AMINO-5-CHLORO-2-ETHOXY-N-ÄÄ4-(4-FLUOROBENZYL)-2-MORPHOLINYL ÜMETHYLÜBENZAMIDE (MOSAPRIDE)' CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 42, no. 4, 1994, pages 877-882, XP002216378 ISSN: 0009-2363

D7: SAKURAI N ET AL: 'Synthesis and structure-activity relationships of 7-(2-aminoalkyl)morpholinoquinolones as anti-helicobacter pylori agents' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 16, 18 August 1998 (1998-08-18), pages 2185-2190, XP004137243 ISSN: 0960-894X

Document D2 was published after the priority date of the present application, and will thus not be taken into consideration for this written opinion.

With regard to the requirement for novelty (Article 33(2) of the PCT), the essential difference between the process of claims 1-3 and that of the prior art D1 is the use of the enantiomer of the compound XXI, with D4 in that although it is stated that optically active starting materials can be used (see page 6, last line), no specific disclosure is made, and from D5 in that the compound XX is not employed. D6 discloses a reaction sequence which differs in that although using the same starting materials as claim 3 of the present application, the intermediate compound 7 is lacking the A group required in the end product IIIB. The separation process of claim 4 differs from D7 and D3 in the use of an enzyme. Article 33(2) of the PCT thus appears to have been satisfied.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the claims 1-3,5 and 4 will be dealt with separately

Claims 1-3,5

For this process for the preparation of the compounds of formula IIIA, the closest prior arts are considered to be D1,D4,D5 and D6. The problem underlying the present application appears to have been the provision of a new process for the preparation of the compounds of formula IIIA. The solution provided y the Applicant is the process of claim 1, with the variant of claims 2 and 3. It is considered that claim 3 is not actually complete, in that the reaction with eg potassium pthalimide is required in order to arrive at a compound of formula IIIB. However, in general, the distinguishing feature vis a vis the prior arts is the use of the enantiomer of compound XXI. It is stated in D4 that the use of optically active starting materials can be used, as well as resolution of the products. Thus, as this process in 4 is the same as the present application, there is already incentive for the man skilled in the art to use active starting materials. Furthermore, D1 describes the exact process, including the intermediate compound 9, and D5 and D6 also use the active epichlorhydrin (albeit in a slightly different reaction scheme). Thus it is considered that the man skilled in the art had sufficient incentive to attempt the process of the present application, and thus the problem must have been the provision of a further process with unexpected advantages re the prior art, and in the absence of any such advantages, Article 33(2) cannot be considered to have been satisfied for claims 1-3 nor for the intermediate of claim 5.

For claim 4, a different problem underlies the invention, namely the process for the separation of a compound of formula IIIAS from its antipode. The only distinguishing feature vis a vis the prior arts D7 and D3 is the use of an enzyme, but this is considered to be only another variant commonly used in the art for resolution, and thus not in itself

inventive. Article 33(2) is thus not satisfied for claim 4.

The reference on page 1 should be to PCT/GB01/04350